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Role of the Extracellular Matrix in Cancer-Associated Epithelial to Mesenchymal Transition Phenomenon

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The epithelial to mesenchymal transition (EMT) program is a crucial component in the processes of morphogenesis and embryonic development. The transition of epithelial to mesenchymal phenotype is associated with numerous structural and functional changes, including loss of cell polarity and tight cell–cell junctions, the acquisition of invasive abilities, and the expression of mesenchymal proteins. The switch between the two phenotypes is involved in human pathology and is crucial for cancer progression. Extracellular matrices (ECMs) are multi-component networks that surround cells in tissues. These networks are obligatory for cell survival, growth, and differentiation as well as tissue organization. Indeed, the ECM suprastructure, in addition to its supportive role, can process and deliver a plethora of signals to cells, which ultimately regulate their behavior. Importantly, the ECM derived signals are critically involved in the process of EMT during tumorigenesis. This review discusses the multilayer interaction between the ECM and the EMT process, focusing on contributions of discrete mediators, a strategy that may identify novel potential target molecules. *Developmental Dynamics 247:368–381, 2018*. © 2017 Wiley Periodicals, Inc.

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Introduction

The epithelial to mesenchymal transition (EMT) program significantly contributes to the processes of morphogenesis and embryonic development. Indeed, the generation of this complex program with simultaneous secretion of extracellular matrices (ECMs), by the cells, gave rise to three-layered triploblasts in the dawn of evolution (Newman, 2016). The evolutionary appearance of epithelial cells contributes to important aspects of tissue and organ formation due to these cells' inherent characteristics, including polarity, the ability to aggregate into sheets, formation of specific cell junctions, intact cell–cell interactions, as well as formation of a basal membrane (Tyler, 2003). Importantly, epithelial cells execute numerous functions, including organ protection, exocrine secretion, liquid absorption, and gas exchange. To perform these functions, epithelial cells form tight junctions and are strongly attached to adjunct ECM.

EMT is a process that converts polarized epithelial cells into motile cells. During EMT, epithelial cells, lose their epithelial characteristics and acquire mesenchymal properties, e.g., morphological modification from arranged cuboidal, columnar, or squamous shape to fibroblast spindle appearance (Thiery et al., 2009; Ingthorsson et al., 2016). The transition involves numerous changes, including loss of cell polarity and tight cell–cell junctions, the acquisition of invasive abilities and the expression of mesenchymal proteins (Hay, 2005; Thiery et al., 2009; Sun and Fang, 2016). The EMT process has significant roles in morphogenesis and homeostasis, facilitating cell differentiation during organ development as well as during adulthood (Tsai et al., 2002; Mercado-Pimentel and Runyan, 2007; Nieto et al., 2016).

EMT, which is inseparably correlated to development of multicellular organisms may, on the other hand, contribute to carcinogenesis (Yeung and Yang, 2017). Indeed, the switch between epithelial and mesenchymal phenotype is directly involved in human pathology and is crucial for cancer progression (Kalluri, 2009). In addition, EMT is closely associated with homeostasis and pathological conditions, including tissue repair and fibrosis (Thiery et al., 2009). Emerging data highlight the complexity of the process and pinpoint to aspects that have not been fully explored (Nieto et al., 2016). Indeed, a high level of plasticity between epithelial and mesenchymal phenotypes has lately been proposed: with cells being in transient "hybrid" states (Nieto et al., 2016).

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It is well established that the process of EMT is a component of embryonic development (Kalluri, 2009; Kalluri and Weinberg, 2009). The generation of the mesenchymal phenotype is imperative for the creation of tissues and for the subsequent formation of organs (Kalluri, 2009; Kalluri and Weinberg, 2009). One should note that the "foundation" of tissue development is the appearance of the mesenchymal phenotype. The primary mesenchyme is formed during the gastrulation stage of embryogenesis, allowing the first distinction between epithelial and mesenchymal cell morphology and facilitating tissue formation (Solnica-Krezel, 2005).

Moreover, the process of embryogenesis is characterized by a dynamic as well as obligatory transition of cells between the two phenotypes (Thiery, 2002; Thiery et al., 2009). Therefore, it seems likely that many or all detected variations of the program have developmental origins and that mechanism of fibrosis or metastases recapitulate this variety rather than the development of new mechanisms. Indeed, in cancer cells, such variations could be due to epigenetic and genetic changes affecting tumor suppression genes and oncogenes (Kalluri, 2009; Kalluri and Weinberg, 2009). Importantly, the EMT is proposed to significantly contribute to the initiation and early growth of primary epithelial cancers (Hanahan and Weinberg, 2000). The concept is that cancer cells may reactivate developmental programs, latent in physiological adult cells, and this reactivation contributes to tumorigenesis by means of inducing increased cell proliferation and resistance to apoptosis (Micalizzi et al., 2010). Moreover, EMT has been suggested as a critical step for cancer progression and malignant metastasis, as cancer cells undergoing this event are able to invade and migrate (Yang and Weinberg, 2008; Strizzi et al., 2009; Ye and Weinberg, 2015). Linkage, however, of EMT to proliferation needs to be taken with caution, as direct correlation is not established and may be contradictory.

We will, therefore, focus on the well-established EMT effects on the motility properties of the cell. EMT, as discussed, involves changes in cell morphology that are imperative in cancer progression, such as the transition between cuboidal to spindle fibroblast-shaped cell (Kalluri and Weinberg, 2009; Micalizzi et al., 2010; Ingthorsson et al., 2016). Moreover, EMT progression includes localized disruption of cell–cell adhesion points, breakdown of the basal membrane, and mass migration (Ingthorsson et al., 2016). Transmembrane proteins play significant roles in EMT as they participate in the formation of cell junctions and are included in adherens junctions. Specifically, cadherins, connect cells by means of homophilic attachments created by their extracellular domains (Cavallaro and Christofori, 2004; Ingthorsson et al., 2016). The expression of N-cadherin (cadherin of neurons and fibroblasts) instead of the expression of E-cadherin (cadherin expressed by epithelial cells) is a characteristic modification in gene expression, during EMT (Peinado et al., 2007; Berx and van Roy, 2009).

Therefore, the cell acquires the ability to move into the ECM and to invade (Chaffer et al., 2007; Kalluri and Weinberg, 2009). However, there needs to be room in the EMT concept to include migration or invasion in cell sheets or as collective migration. One such example is neural crest cell migration, which can be defined as the coordinated migration of cells in sheets or loose groups (Etienne-Manneville, 2014). In these migrating collectives, the cadherin-based cell contacts were thought to control cell–cell attachment, but now it is understood that cadherin-based cell contacts are also crucial mediators of a sensitive molecular communication that facilitates cell polarization and collective migration with specific directionality (Carmona-Fontaine et al., 2008; Friedl and Gilmour, 2009).

Indeed, the delicate balance in E-cadherin/N-cadherin expression determines, to a large extent, these cells' directional locomotion (Carmona-Fontaine et al., 2008). Other transmembrane proteins, which participate in the formation of strong junctions between epithelial cells, are occludin and claudin junctions. During EMT, these proteins' expression are altered in a manner dependent on the cellular context and on the particular claudin considered (Moustakas and Heldin, 2007).

During EMT tumor cells acquire cancer stem cell like properties and therapeutic resistance; thus, EMT facilitates tumor cell invasion, spread, and metastasis (Reya et al., 2001; Thiery et al., 2009). Therefore, one can conclude, that the activation of EMT is a critical step for acquisition of malignant phenotype by epithelial cancer cells (Thiery, 2002; Polyak and Weinberg, 2009). However, full EMT transition is not necessary as cell exhibiting intermediate hybrid epithelial and mesenchymal phenotypes "partial EMT" phenotype (Abell et al., 2011; Huang et al., 2013) have been characterized as "metastable" (Tam and Weinberg, 2013; Nieto et al., 2016). Indeed, "partial EMT" phenotype has also been described during morphogenesis (Futterman et al., 2011). It is noteworthy that, in some cases, the metastatic ability of cancer cells is not directly correlated with genotypic and phenotypic properties of EMT per se, which indicate that separate functions may regulate the ability of cancer cells to metastasize (Lou et al., 2008).

Extracellular Matrix Organization

The ECMs, defined as multi-component networks that surround cells in tissues, are obligatory for cell survival, growth, and differentiation as well as tissue organization (Hynes, 2009). The deposition of ECM is one of the hallmarks of metazoa (Exposito et al., 2010) and embedded in the very essence of the evolution process (Ozbek et al., 2010). Fine structural studies have disclosed that the ECMs are rich in proteins, including proteoglycans (PGs), collagens, and laminins, as well as glycosaminoglycans (GAGs); and that these components are organized in domains. GAGs are linear, negatively charged polysaccharides, classified to four types: hyaluronan (HA), chondroitin sulfate (CS) and dermatan sulfate (DS), heparin and heparan sulfate (HS), as well as keratan sulfate (KS). These polysaccharides, with exception of HA are able to covalently bind to protein cores which leads to formation of PGs.

Moreover, GAG chains modulate PG biological roles in a type-dependent manner (Nikitovic et al., 2008b, 2014a; Chalkiadaki et al., 2009; Karamanos and Tzanakakis, 2012). It is noteworthy, that free GAGs may execute discrete effects on tumor cell functions depending on their phenotypes (Syrokou et al., 1999). The GAG hyaluronan is an important ECM component, bestowed with both mechanical, such as water retention, and regulatory properties that contribute to different cell functions. It is thus surprising, that HA is structurally a simple polymer of disaccharides composed of alternating N-acetylglucosamine (GlcNAc) and glucuronic acid (GlcA) units in the 5000–20,000,000 Da molecular mass range (Weigel et al., 1997). HA is synthesized by three types of transmembrane proteins denominated hyaluronan synthases: HAS1, HAS2, and HAS3 (Vigetti et al., 2015).

On the other hand, the degradation of HA within tissues, is accomplished by enzymes denominated as hyaluronidases (HYAL) of which seven have been identified in humans (Jiang et al., 2011). Importantly, as regarding HA "size matters," as this simple molecule exhibits complex regulatory functions in a size-dependent manner (Jiang et al., 2011). Thus, oligosaccharides that result from HA degradation and low-molecular-weight HA (LMWHA) are capable of initiating angiogenesis and inflammation. On the other hand, high-molecular-weight HA (HMWHA) (1000–2000 kDa), which facilitates homeostasis, is present in intact tissues and is antiangiogenic as well as immunosuppressive (West et al., 1985; Jiang et al., 2011; Kavasi et al., 2017).

PGs are composite molecules in which a GAG chain(s) is covalently bound into a protein core. The most updated nomenclature categorizes the 43 known mammalian PGs into four classes: the intracellular, cell-surface, pericellular, and extracellular PGs. The enlistment of PGs to classes is based on the following criteria: cellular and subcellular location, overall gene/protein homology, and the use of specific protein modules within their respective protein cores. It must, however, be mentioned, that there is a great deal of overlapping among the classes (Iozzo and Schaefer, 2015). The only to date identified intracellular PG is serglycin, unique moreover, in its ability to covalently bind heparin side chains (Douaiher et al., 2014). Most cell-surface PGs, which are either transmembrane proteins or are anchored to cell membrane by means of glycosyl-phosphatidyl-inositol (GPI) contain HS chains (Tumova et al., 2000; Afratis et al., 2017). These molecules engage in interactions with various extracellular ligands, including growth factors, growth factor receptors frizzled and slit/robo, as well as adhesion molecules to modulate basic cellular functions (Couchman et al., 2015).

Pericellular PGs are likewise mostly HSPGs including perlecan, agrin, collagens XV and XVIII. An outstanding PG member is perlecan, which sequesters several HS binding growth factors (e.g., fibroblast growth factor [FGF], platelet derived growth factor [PDGF], vascular endothelial growth factor, and CTGF) to the pericellular space and thus facilitates cell signaling (Melrose et al., 2008). This PG simultaneously engages other ECM proteins to stabilize the ECM structure and in the case of epithelial cells significantly contributes to the formation of the basement membranes. The extracellular PGs are grouped to two major families: the hyaluronan and lectin-binding PGs (hyalectans) and the small leucine-rich PGs (SLRPs) (Iozzo and Murdoch, 1996). Hyalectans such as versican are mostly decorated with CS side chains (Wight, 2016). These PGs interact with HA creating superstructures that facilitate cell proliferation, migration, and survival.

Furthermore, hyalectans may also act as molecular bridges connecting cell surface to matrix (Mecham, 2012; Wight, 2016). The SLRPs were originally defined as PGs with a relatively small protein core (36–42 kDa) bearing tandem leucine-rich repeats. Their small protein cores exhibit numerous posttranslational modifications, including substitution with GAG side chains of various types and binding of oligosaccharides (Iozzo and Murdoch, 1996; Iozzo, 1997). In addition to their ECM deposition the SLRPs are also distributed to the pericellular place as previously discussed (Nikitovic et al., 2012). The "far away from the cell surface" deposited SLRPs bind to various types of collagens, thereby regulating the kinetics, assembly, and special organization of fibrils in skin and connective tissue (Reed and Iozzo, 2002; Zhang et al., 2006).

The deposition of the SLRPs to pericellular matrix allows these PGs to interact with different ligands and cell-surface receptors. This interplay results in the regulation of multiple cell–matrix interactions as well as downstream signaling pathways (Iozzo and Schaefer, 2010). The involved signaling mediators including transforming growth factor–beta (TGF-β), PDGF, bone morphogenetic proteins (BMPs), insulin-like growth factor I (IGF-I) as well as, among other, EGF receptor and ErbB4 are analytically discussed by Iozzo and Schaefer (2010). Taking into account that the synthesis, turnover, and final localization of the SLRPs are dynamic processes, variable SLRP availability at different compartments modulates signaling pathways responsible for specific biological and pathological processes (Merline et al., 2009; Nikitovic et al., 2011, 2014a). Therefore, in conclusion, PGs are endowed with specific characteristics which enable them to modulate "out-in" and "in-out" signaling including that of growth factors and cytokines that regulates various cellular functions, such as, growth, migration, and invasion, and are closely correlated to tumorigenesis (Theocharis et al., 2015; Pozzi et al., 2016).

Collagens are a group consisting of twenty eight ECM molecules (Coll I-XXVIII), crucial in ensuring the structural integrity of cells and tissues (Kadler et al., 2007, 2008). These trimeric molecules consisting of three α chains are obligatorily woven together into a triple helix in at least one region. In each α chain, the triple helical regions, termed Col domains, are flanked by noncollagenous (NC) domains. Importantly, the NC domains contain specific peptide modules recognized by other matrix molecules that bestow complex functions to collagens in both health and disease (Kassner et al., 2003; Kadler et al., 2007, 2008; Gordon and Hahn, 2010). Thus, in addition to their structural role collagens are regulators of active mediators such as BMPs or HA affecting their bioavailability at different locations (Karousou et al., 2014; Sedlmeier and Sleeman, 2017).

The ECM suprastructure provides the bulk, shape, and strength of tissues in vivo as reviewed by Hynes (2009). The organization of ECM molecules into domains actually supports conserved structure–function relationships, including oligomerization of collagen domains, recognition of specific cell membrane receptors by fibronectin (FN), or the binding of SLRPs to collagen regulating, thus, the local concentration or accessibility of cytokines (Hynes, 2009; Nikitovic et al., 2012). It must, however, be highlighted that the ECM is a dynamic structure where, under physiological conditions, the processes of degradation and deposition are finally balanced to facilitate homeostasis. The family of endopeptidases, matrix metalloproteinases (MMPs), is a key player in these processes. MMPs degrade ECM components in a highly directed manner, which results in the release of bioactive fragments and growth factors in addition to the modulation of the ECM architecture, all of which influence cellular behavior (Mott and Werb, 2004). Thus, MMPs have become a focal point for understanding matrix biology. In conclusion, the extremely well-organized ECM suprastructure can by means of a specific spatial pattern process deliver a plethora of signals to cells that ultimately regulate their behavior. Subsequently, the ECM is critically important for cell growth, survival, differentiation, and EMT, as well as key to various disease processes including cancer (Hynes, 2009; Kessenbrock et al., 2010; Nikitovic et al., 2012)

ECM Remodeling During Carcinogenesis

The growth and morphogenesis of epithelia is under the influence of the surrounding stroma. The stroma is composed of ECM rich in collagen and stromal cells like fibroblasts, immune cells, adipocytes and endothelial cells (Ronnov-Jessen et al., 1996). Indeed, the ECM represents a "big tank" of potential regulators of cancer cell fate, including growth factors, glycoproteins, PGs, and MMPs (Nikitovic et al., 2012; Skandalis et al., 2014). Specifically, changes in ECM composition and interactions between ECM components and tumor cells modify numerous cancer cell functions (Nikitovic et al., 2013; Nikitovic et al., 2014a,b). Basic components of ECM, such as FN and collagen, are very important for cancer progression (Pankov and Yamada, 2002; Imamichi and Menke, 2007; Kirkland, 2009). Furthermore, studies by our laboratory suggest that GAGs and PGs have key roles in the regulation of cancer cell properties, including proliferation, invasion, and motility, through fine regulation of the binding affinity between active ligands and their respective cell membrane receptors (Chalkiadaki et al., 2011; Nikitovic et al., 2012; Mytilinaiou et al., 2013).

Collagens have been shown to be overproduced in several malignancies as is the case for type I and III collagens in pancreatic cancer (Aoyagi et al., 2004), collagen XVIII in lung cancer (Liu et al., 2016), or collagen type I in medulloblastoma (Liang et al., 2008). Numerous studies attribute a significant role for collagen type I, a major constituent of stroma, on cancer cell motile properties and EMT (Sherman-Baust et al., 2003; Shintani et al., 2006; Kirkland, 2009; Martins et al., 2009; Iseri et al., 2010; Li et al., 2010; Cheng and Leung, 2011; Chen et al., 2012; Januchowski et al., 2014). Indeed, the remodeling of collagen-I enriched ECM with the evolution of the "desmoplastic reaction" is a "hallmark of majority of cancer types including pancreatic ductal adenocarcinoma" (Shields et al., 2012; Tian et al., 2015).

Furthermore, collagen-1A1 isoform has been identified as an important contributor to non–small-cell lung cancer progression (Ezzoukhry et al., 2016). Likewise, the crosslinking of collagen-1, driven by TGF-β action, facilitates invasion of hepatocellular carcinoma cells (Ezzoukhry et al., 2016). Moreover, a positive correlation of collagen-1 expression with bladder cancer progression has been established (Brooks et al., 2016). Indeed, several studies propose that the "stiffness" of the matrix, largely determined by collagen crosslinking or organization of the FN matrix contributes to the initiation of EMT (Barker et al., 2014). Wei et al. suggest that in breast tumors, the presence of dense clusters of collagen fibrils, indicating increased matrix stiffness, initiates a TWIST1-dependent EMT which promotes tumor invasion and metastasis (Wei et al., 2015). In human breast tumors, collagen fiber alignment, a marker of increasing matrix stiffness, predicts poor survival. Therefore, the ECM can through a mechanotransduction pathway initiate EMT to facilitate invasion and metastasis.

In addition to the role in mechanotransduction, the alterations in the structure/expression of FN modulate key biological functions through specific cell as well as matrix component binding sites of this molecule (Wang et al., 2016a,b). Noteworthy, FN is a mesenchymal marker, whose expression is increased in EMT and is usually correlated with tumor migration and metastasis (Rafael et al., 2015). Jung et al. (2015) discuss that FN is an ECM constituent that regulates EMT, supporting local invasion and metastatic dissemination. Thus, FN facilitates the activation of signaling pathways crucial for cancer progression (Ioachim et al., 2002; Balanis et al., 2013). Noteworthy, specific modifications in FN structure are directly correlated to the onset of EMT. An illustrative example is that the expression of the FN splicing isoform EdB, specific for tumor tissues, is suggested to be a marker of EMT in translational oncology (Petrini et al., 2016; Yi et al., 2016).

HA, in contrast to other GAGs, is not sulfated (Weigel et al., 1997; Tammi et al., 2008). It is synthesized by hyaluronan synthases (HAS) de novo (Viola et al., 2015) and degraded by hyaluronidases (HYALs) (Stern, 2008). HA is usually overexpressed in solid tumors and correlated to processes facilitating tumorigenesis (Karousou et al., 2014; Nikitovic et al., 2015). Thus, as discussed by Karousou et al., both HA and collagen VI are overexpressed in breast cancer, creating an environment that facilitates tumorigenesis and metastastic dissemination. These effects are correlated to enhanced inflammation and angiogenesis due to increased recruitment of macrophages and endothelial cells (Karousou et al., 2014).

PGs can be found secreted to the ECM, cell-surface associated as well as intracellularly deposited (Iozzo, 1998; Schaefer and Schaefer, 2010; Theocharis et al., 2016). Cell-surface PGs are divided into two groups: syndecans and glypicans (Iozzo, 1998; Afratis et al., 2017). The expression levels of syndecans are reported to change considerably during cancinogenesis suggesting their use as prognostic markers, or indicating their role in the initiation and progression of malignant diseases (Afratis et al., 2017). Thus, syndecan-1 and -2, are important in the regulation of motility (Mytilinaiou et al., 2013; Afratis et al., 2017) and have been identified as prognostic markers in breast carcinoma as well as in oral tongue squamous cell carcinoma progression (Loussouarn et al., 2008; Vered et al., 2010).

Indeed, discrete syndecan-1 regions have been shown to modulate the biological functions of mesenchymal tumors (Zong et al., 2011). PGs secreted to the ECM are hyalectans, SLRPs, and basement membrane PGs. Extensive changes in these PG expression have been noted, among other, during breast cancer progression and correlated to breast cancer cell signaling, survival as well as migration (Theocharis et al., 2015; Pozzi et al., 2016). The only characterized intracellular PG is serglycin, and it has been detected in some cancer tissues including breast cancer (Korpetinou et al., 2013, 2014). Furthermore, serglycin was found to be highly expressed and constitutively secreted at high levels in more aggressive lung, breast, prostate, and colon cancer cell lines (Korpetinou et al., 2015).

Decorin and lumican are SLRPS usually secreted by the cells to ECM. These PGs interact with growth factors including those of the TGF superfamily, BMPs, as well as the EGF family. The aforementioned interactions allow the SLRPs to ultimately regulate their action under physiological conditions and cancer (Iozzo, 1998; Schaefer and Schaefer, 2010; Theocharis et al., 2010; Zafiropoulos et al., 2010). Latest data suggest a significant contribution of the PG to the processes of tumor-associated inflammation and autophagy, as elegantly discussed by Iozzo and Schaefer (2015).

The activity of MMPs is of critical importance in the process of tissue remodeling during cancer progression (Gialeli et al., 2011; Nikitovic et al., 2013). Indeed, MMP activity contributes crucially both to tumor growth and to the metastatic cascade including proteolytic degradation of the ECM, modifications of the cell–ECM and cell–cell interactions, motility as well as angiogenesis (Hotary et al., 2003).

Discussion

Roles of ECM in Cancer-Related EMT

Research efforts in the field of cancer biology have demonstrated a key participation of ECM-dependent cues. Importantly, the ECM is both affected by, as well as inherently involved in the cancer-associated EMT. ECM components through fine orchestration of EMT-regulating pathways significantly affect its execution.

Collagen-Dependent EMT Events in Cancer

Important examples are the collagen-I-dependent EMT effects in cancer. Thus, in vitro experiments on human colorectal carcinoma cells revealed induction of EMT, when these cells were cultured on a collagen substrate (Kirkland, 2009). Indeed, the morphology of these cells was altered, acquiring a flatter shape with less cohesiveness in parallel with a down-regulation of E-cadherin and β-catenin deposition at intracellular junctions. Furthermore, the differentiation of human colorectal carcinoma cells was inhibited and their increased clonogenicity evident (Kirkland, 2009).

In PC3 prostate and SKOV3 ovarian cancer cells, the important epithelial cell marker E-cadherin was likewise found to be down-regulated, when these cells were cultured on a collagen type I substrate (Cheng and Leung, 2011). Indeed, these authors specify that the effect of collagen-I was executed through transcriptional up-regulation of the E-cadherin repressors Snail and Slug (Cheng and Leung, 2011). Specifically, the E-cadherin down-regulation was modulated by PI3K/Akt signaling pathway, demonstrated through the usage of siRNA specific for PI3K, which partially abrogated the collagen-I effect (Cheng and Leung, 2011). Moreover, collagen I is suggested to down-regulate E-cadherin expression by means of two different mechanisms where the long-term mechanism targets gene expression of E-cadherin through c-Scr kinase and the short-term one weakens its adhesion complex, as discussed by Imamichi and Menke (2007).

Furthermore, as argued, cytoplasmatic catenins associated to the E-cadherin complexes exhibit changed tyrosine phosphorylation, which facilitates the disassembly of the adhesion complex. Indeed, as these authors note, the key molecular events participating in collagen-induced EMT include activation of integrins with the subsequent transactivation and translocation of the focal adhesion kinase (FAK) to the complex formed between E-cadherin and β-catenin (Imamichi and Menke, 2007). In normal human pancreatic cells and in mammary epithelial cells, collagen type I up-regulates N-cadherin expression, established to facilitate tumor growth (Shintani et al., 2006, 2008a). As demonstrated in pancreatic cells by these authors, collagen-I interacts with its alpha2-β1integrin and discoidin domain receptor (DDR) receptors to activate FAK-related protein tyrosine kinase (Pyk2) as well as FAK whose downstream signaling converges to enhance N-cadherin expression.

In the mouse mammary epithelial cells model Shintani et al. (2006) had demonstrated that the collagen I-dependent increase in N-cadherin expression was executed through an integrins/PI3K/Rac1/JNK axis. In gastric cancer cells, a similar, promoting role of collagen type I on cell migration and metastasis, through collagen-dependent cytoskeleton reorganization and reduction of cell–cell adhesion, has been described by Li et al. (2010). Specifically, collagen type I induces tyrosine phosphorylation of β-catenin and this event leads to the dissociation of β-catenin and E-cadherin from actin cytoskeleton with consequent entry of β-catenin to cell nucleus and concomitant gene expression regulation; these events ultimately result in enhanced transcription of growth-promoting genes (Li et al., 2010).

Likewise, seeding of MCF-7 cells in three-dimensional (3D) collagen scaffolds generates a cell population with more pronounced cancer stem cell properties; e.g., up-regulation of EMT biomarkers and down-regulation of epithelial cell markers (Chen et al., 2012). Collagen type I, participates significantly in *out-in* activation of TGF-β3 signaling and subsequent EMT of lung cancer cells (Shintani et al., 2008b). Importantly, these authors report that the effects of collagen type I are dependent on PI3-kinase and extracellular regulated kinase1/2 (Erk1/2) activities as their downstream signaling promotes the transcription of the TGF-beta3 gene.

The main conduits of EMT-related collagen effects are integrins as shown in melanoma and pancreatic cancer cells (Girotti et al., 2011; Duan et al., 2014). Thus, Duan et al. (2014) specify that the collagen I-dependent promotion of the EMT phenotype in pancreatic cancer cells, including the overexpression of vimentin and N-cadherin, the down-regulation of E-cadherin, as well as the enhanced proliferation and lower apoptotic rate, were mediated by β1-integrin. Indeed, β1-integrin down-regulation abolished the repercussions prompted by collagen I and inactivated the FAK/Akt/ Erk axis; thus, efficiently blocking EMT. Interestingly, the above axis converges onto Gli-1, a Hedgehog pathway protein, suggesting the existence of a cross-talk between Hedgehog and β1-integrin signaling (Duan et al., 2014).

An early study in rat bladder carcinoma cells, demonstrated that α2β1 integrin was found to be an essential mediator for collagen type I-induced cell spreading (Valles et al., 1996). Moreover, in colorectal cancer cells it was concluded that collagen-I is responsible for promoting stem cell characteristics in cancer cells through α2β1 integrin pathway (Kirkland, 2009). Specifically, a strong attenuation of E-cadherin and β-catenin expression at cell–cell junctions with concomitant up-regulation of CD133 and Bmi1 specific stem cell markers, was demonstrated. Other collagen forms are also associated to EMT as is the case of basement membrane collagen type VII whose up-regulation increases invasive behavior of cutaneous squamous carcinoma cells (Martins et al., 2009). A more recent study on lung cancer, revealed a potent role of collagen XVII in EMT, as overexpression of collagen XVII seems to be necessary for EMT phenotype (Liu et al., 2014). Collagen XVII is a type II transmembrane protein located on hemidesmosomes that link epithelial cells with the basement membrane. Its ability to induce EMT is mediated by stabilization of laminin-5 and also increased expression of Snail through FAK/AKT/GSK3b signaling pathway (Liu et al., 2014). The collagen I-dependent signaling, which facilitates the process of EMT, is schematically presented in Figure 1.

FN a Source of EMT-Regulating Cues

The glycoprotein, FN is another important source of EMT-regulating cues. Specifically, a FN-dependent activation of β1-integrin leading to FAK/JAK2/STAT3 signaling pathway activation has been described (Balanis et al., 2013). In lung and in mammary epithelial cancer cells, EMT is partially mediated by increased FN expression (Jia et al., 2010; Park & Schwarzbauer, 2014). Intracellularly, FN induces an EMT response with up-regulation of Snail, N-cadherin, vimentin, MMP-2, and p-Smad2 (Park and Schwarzbauer, 2014). Moreover, FN signaling in mammary and lung cancer cells depends on Src, Erk1/2, and PI3-K, and is correlated to decreased E-cadherin expression (Park and Schwarzbauer, 2014; Sun et al., 2014). A molecular approach in the regulation of mesenchymal genes' expression, such as FN, is suggested by Stanisavljevic et al., (2011). Specifically, Snail1

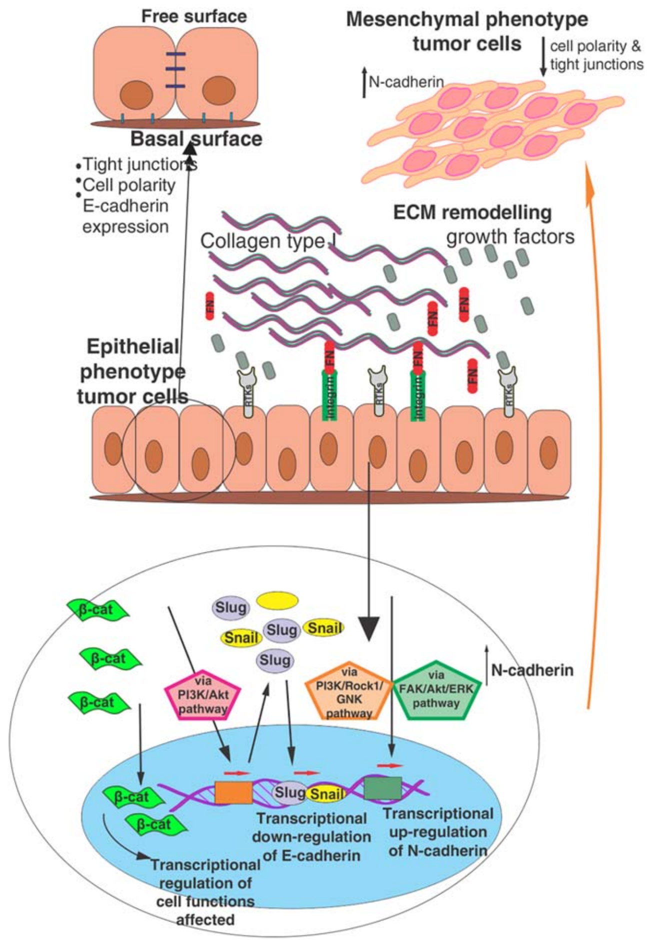

Fig. 1. Interplay among the ECM components and cells during the EMT process. Tumor cells widely interact with the components of the remodeled ECM during the process of EMT. Interactions of ECM components and released active mediators with cell surface receptors, including integrins and tyrosine kinase receptors, activate intracellular signaling initiate transcriptional regulation of the EMT program.

with p65 subunit of NF-kB and PARP1 bind to the FN promoter, inducing FN expression (Stanisavljevic et al., 2011). This mechanism seems to be active in the regulation of expression of other ECM genes involved in cell motility such as HAS2, THBS1 and LAMB3.

Treatment of human prostate epithelial cell lines with TGF-β resulted in the expression of oncofetal FN (fibronectin carrying O-GalNAc at a specific site) with concomitant induction of EMT (Freire-de-Lima et al., 2011). Indeed, oncofetal FN, expressed by embryonic cells and in cancer cells, but not in normal adult tissues, was found to have a synergistic effect with TGF-β1 in EMT initiation (Freire-de-Lima et al., 2011; Ding et al., 2012; Park and Schwarzbauer, 2014). An interesting role for FN in breast cancer cell differentiation was recently reported (Bouris et al., 2015). Thus, down-regulation of the estrogen-related receptor (ERα) in MCF-7 cells resulted in an EMT-like phenotype with the transfected cells overexpressing EMT related molecules including MT1-MMP, MMP1, MMP2, MMP7, FN, vimetin, ZEB1, and SNAIL2/SLUG (Bouris et al., 2015). Overall, silencing of ERα was enough for the creation of a new cell line with mesenchymal phenotype and differential expression of ECM components when compared with parental cells (Bouris et al., 2015).

Moreover, in triple-negative breast cancer (TNBC), the estrogen related receptor α (ERRα) is negatively correlated with FN and EMT (Wu et al., 2015b). Of interest, ERα has the ability to bind to the FN promoter and to positively regulate its transcription. In vitro inhibition of ERα results in diminished cellular motility decreased FN and vimentin expression and inhibited EMT (Wu et al., 2015b). In contrast, increased ERα enhances invasion and migration. In vitro experiments on the FN matrix with prostate cancer cells revealed suppression of FN-induced EMT by the transmembrane protein CD82 (Lee et al., 2017). Therefore, based on these reports, one can conclude that the increased expression of FN is a marker of tumor aggressiveness as well as being a well-established marker for the EMT process (Ignotz and Massague, 1986; Ioachim et al., 2002; Park and Schwarzbauer, 2014).

PGs and EMT Related Events

The alteration of PG composition has been strongly correlated to cancer progression (Nikitovic et al., 2008b; Baghy et al., 2016). It is well established that the SLRP member, decorin binds to TGF-β and constitutes an important regulator for the modulation of TGF-β bioavailability, acting by means of the formation of TGF-β/decorin complex (Hildebrand et al., 1994; Hausser et al., 1996). This function of decorin has an application in EMT as decorin inhibits EMT induced by TGF-β1 through blocking the Erk signal transduction pathway (Wang et al., 2010). Indeed, genetic down-regulation of the decorin gene in the mouse model resulted in the presentation of gastrointestinal tract neoplasms with decreased expression of E-cadherin and the facilitation of the β-catenin signaling (Bi et al., 2008).

The same authors, in continuation, presented data showing direct correlation between decorin stabilization of the E-cadherin complex and attenuation of colon cancer growth and motility (Bi et al., 2012). Lumican seems to be a potent inhibitor of EMT, as Wu et al. (2011) show that this SLRP is transcriptionally inhibited by HMGA2 and its expression is lost in high-grade serous papillary carcinoma. A preventive role for hyalactan, versican 2, has been proposed in tumor cell lines, as up-regulation of this PG leads to suppression of EMT-related transcription factors' expressions through EGFR/Erk/GSK3-β (Lee et al., 2015a). Indeed, versican has been correlated with the opposite to EMT, the process of mesenchymal–epithelial transition (MET) (Soltermann et al., 2008; Gao et al., 2012).

The cell membrane PGs have a distinct role in EMT processes. Early reports suggested that the loss of cell surface syndecan-1 induces epithelial cells to transform into anchorage-independent mesenchyme-like cells (Kato et al., 1995). Later reports have demonstrated a coordinated loss in E-cadherin and syndecan-1 expression in various epithelial cancer types, including colorectal cancer and acantholytic squamous cell carcinoma. The down-regulation of the two mediators was associated to the phenotypic transformation of the respective cancer types (Day et al., 1999; Bayer-Garner and Smoller, 2001; Mitselou et al., 2016). Moreover, in colon cancer, syndecan-1 expression was negatively correlated to stage and metastasis to local lymph nodes but was not correlated with patient survival outcomes (Hashimoto et al., 2008).

A study in prostate cancer suggested a correlation between synthesis of syndecan 1 and 2 and the modulation of the EMT markers E-cadherin and β-catenin (Contreras et al., 2010). In addition to the regulation of E-cadherin levels, it has been suggested that the transcription suppressor SNAIL, crucial in EMT, attenuates the expression of syndecan-1 in prostate cancer (Poblete et al., 2014). In a separate study performed in the same prostate cancer model, syndecan-1 was found to increase microRNA-331-3p and to mediate EMT through specific regulation of vimentin, snail, and N-cadherin, as well as of E-cadherin and desmoplakin expressions (Fujii et al., 2016). Moreover, overexpression of syndecan-2 in a human colorectal adenocarcinoma cell line (HT29) through stimulation of MMP-7 facilitated the proteolytic shedding of E-cadherin and the acquiring of the mesenchymal phenotype by these cells (Jang et al., 2016).

Indeed, the heparanase/syndecan 1 axis seems to be an important pathway of the tumor-derived exosomes (TDEs) which carry a pro-EMT program (Syn et al., 2016). Glypican-3, a member of the glypican HSPG family, is suggested to be an inducer of the EMT program in hepatocellular carcinoma cells, through Erk1/2 signaling pathway (Qi et al., 2014; Wu et al., 2015a). Importantly, the expression of PGs by both normal and tumor cells is regulated by growth factor action (Tzanakakis et al., 1997).

MMP-Derived Signals in the EMT Program

It is now well established, as comprehensively discussed by Brooks et al. (2016), that the initial stages of localized tumor invasion require proteolytic processing of the ECM to override tissue barriers during basement membrane and interstitial tissue transmigration programs. The released matrikines affect various cellular functions, including the inappropriate activation of the EMT program, which can contribute to cancer progression (Nistico et al., 2012). Importantly, even in early studies, EMT-like events have been correlated to increased expression/activity of MMPs and resulting matrix degradation (Bae et al., 1993). Thus, Lochter et al. (1998) report in a mammary epithelia cell model that MMP stromelysin-1 (SL-1) initiates an epigenetic molecular program in mammary epithelial cells that culminates in various phenotypic modulations that finally result in the acquiring of a malignant tumor-cell phenotype.

Moreover, these “pioneer” studies suggest that only breast cancer cells that have acquired the “fibroid phenotype” express the membrane type 1 MMP (MT1-MMP), which is an activator of MMP-2 responsible for ECM degradation (Pulyaeva et al., 1997). Noteworthy, increased activity/expression of MT-MMP is involved in several cancers, including prostate (Udayakumar et al., 2003; Haage et al., 2014), glioblastoma (Munaut et al., 2003), lung (Zhou et al., 2014), as well as in gastric cancer tissues (Li et al., 2015b). In continuation, it was revealed that MMPs have a causal role in cancer as stromelysin-1/MMP-3, a stromal enzyme up-regulated in many breast tumors, was found to induce EMT and malignant transformation in vitro through a Rac1/reactive oxygen species axis (Radisky et al., 2005).

Moreover, the increased expression of MT1-MMP was positively correlated with EMT in gastric cancer (Li et al., 2015b). These authors show that an in vitro knockdown of MT1-MMP decreased migration and invasion as well as reduction of EMT related genes including vimentin, snail, slug, and ZEB1 in gastric cancer cells (Li et al., 2015b). Additionally the knockdown of MT1-MMP down-regulated the expression of MMP2, MMP9, MMP13, in agreement with previous studies on other malignancies (Sato et al., 1994; Knauper et al., 1996; Nishida et al., 2008; Chellaiah and Ma, 2013).

The feedback between MMPs’ expression levels was also evident in a study where upon MT-MMP1-mediated activation of MMP13, several ECM components are degraded including FN (Sato et al., 2005). Orlichenko and Radisky (2008) provide a comprehensive overview of how tumor-associated MMPs can facilitate processes contributing to EMT. On the other hand, the exquisite feedback between EMT events and ECM was indicated even in an early study showing that collagen type I induced MT1-MP expression and MMP-2 activity during breast cancer metastasis (Gilles et al., 1997). The complexity of the feedback is highlighted by a recent study in hepatocellular carcinoma where it is shown that a PI3/Akt/MMP-7/syndecan 1 axis initiated TGF-β dependent EMT (Zeng et al., 2016). Another aspect of the ECM input in cancer associated EMT is the putative transdifferentiation of nonmalignant epithelial or epithelial-derived carcinoma cells to myofibroblasts of the tumor stroma, due to signaling initiated by MMPs’ activities (Bissell et al., 2005).

HA Metabolism and EMT in Cancer

HA is likewise reported to facilitate the process of EMT (Camenisch et al., 2000; Heise et al., 2011; Koistinen et al., 2016), but it is less investigated than its protein ECM constituent counterparts. Chow et al. (2010) revealed a potent role of HA in EMT of epithelial-phenotype cancer cells by up-regulating HAS3. HAS3 is one of the three mammalian HA synthases that is usually overexpressed in malignancies (Adamia et al., 2005) or inflammation (Kavasi et al., 2017). Not only was the epithelial-like morphology of HAS3-overexpressing cells transformed into a mesenchymal-like one, but also, E-cadherin was decreased, while their vimentin expression was enhanced (Chow et al., 2010). A noteworthy correlation between E-cadherin and HA, is the negative modulation of E-cadherin during the process of HA-CD44 binding (Xu and Yu, 2003).

In fact, overexpression of E-cadherin weakens the affinity between the receptor and the ligand, whereas a decrease of E-cadherin enhances tumor progression (Xu and Yu, 2003). Interestingly, discrete CD44 isoforms, due to alternative splicing, were found to be correlated with EMT (Heldin et al., 2014; Cieply et al., 2015). Thus, EMT is associated with the obtained resistance to anoikis in a subtype of aggressive cancer cells, through the obligatory participation of the CD44S isofom-HA interactions (Cieply et al., 2015). Moreover, it is noteworthy that CD44S is a cancer stem cell marker (Cieply et al., 2015). Importantly, the modifications of alternative splicing procedure in favor of the CD44S and against the CD44V isoform, not only is essential for EMT, but also promotes breast malignancies in mice (Brown et al., 2011). In fact, the expression of the CD44S isoform, to which a higher affinity for HA is attributed, seems to prevail in cells which have undergone or are in the process of EMT (Heldin et al., 2014; Cieply et al., 2015). The Snail transcription factor, which has a key role in EMT, attenuates the transcription of the epithelial splicing regulatory protein 1 (ESRP1), which is a positive regulator of alternative splicing resulting in the CD44V isoform synthesis (Reinke et al., 2012).

Interestingly, collaboration between TGF-β, a known EMT inducer, and HA pathways has been suggested. Thus, TGF-β induces EMT, through HAS2 up-regulation in NMuMG mammary epithelial cells (Porsch et al., 2013). In fact, knockdown of HAS2 not only significantly decreased EMT but also ameliorated TGF-β–induced cell migration (Porsch et al., 2013). Furthermore, TGF-β seems to affect CD44 alternative splicing, by down-regulating ESRP expression (Horiguchi et al., 2012). Notably, TGF-β is a factor key to the preserving of the mesenchymal-like phenotype in circulating cancer cells, due to CD44S isoform downstream signaling, which regulates vimentin and Smad2 levels (Mima et al., 2012) and as discussed by Heldin et al. (2014). Furthermore, Ouhtit et al. (2013) suggest that HA/CD44s signaling, which initiates ATF/CREB activity, might facilitate TGF-β2 transcription.

ECM Components Affect Central Signaling Pathways of the EMT Program

Numerous signaling pathways and intracellular mediators have been identified in cancer-related EMT processes (Lopez-Novoa and Nieto, 2009). Importantly, these pathways are highly responsive to cues originating from the ECM (Hanahan and Weinberg, 2011). Specifically, TGF-β, PDGF, hepatocyte growth factor, and FGF acting by means of RTKs and intracellularly through Ras-Raf- MAPK, or PI3K, β-catenin, and nuclear factor κ-B pathways are referred as EMT inducers (Savagner et al., 1997; Boyer et al., 1999; Huber et al., 2005; Grotegut et al., 2006; Tavares et al., 2006; Hanahan and Weinberg, 2011). Indeed, growth factors including TGF-β, either as soluble components of ECM or bound to various ECM molecules and released by ECM turnover are major regulators of the EMT program. TGF-β1 is a main EMT-inducing growth factor (Gordon et al., 2008; Andarawewa et al., 2011; Kamitani et al., 2011; Sengupta et al., 2013) which activates EMT transcriptional regulators, such as Snail, Twist and Zinc finger E-box bonding homeobox 1 (ZEB1) (Argast et al., 2011; Porsch et al., 2013).

It is suggested that TGF-β is a crucial contributor of EMT in different cancer types, such as mouse mammary carcinomas and liver and colon cancers (Oft et al., 1998; Lehmann et al., 2000; Gotzmann et al., 2002; Ingthorsson et al., 2016). Upon ligand binding to TGF-β respective type I and type II receptors (serine/threonine kinase activity), a phosphorylation of cytoplasmic Smad family proteins is executed as well as the consequent entry of Smad4 to the nucleus and regulation of target genes' expression (Massague et al., 2005). It is noteworthy that ECM components, such as SLRPS, can regulate both TGF-β ligand accessibility and receptor activation during the insidious process of carcinogenesis (Nikitovic et al., 2008a,b, 2011).

In continuation, TGF-β signaling pathway activation results in down-regulation of epithelial proteins, E-cadherin, ZO-1 (tight junction protein), and keratins, and at the same time up-regulates mesenchymal markers such as FN, fibroblast specific protein 1, α-smooth muscle actin, and vimentin (Pardali and Moustakas, 2007). Actually, the TGF-β–dependent regulation of transcription that affects EMT includes numerous target genes and transcriptional factors as reviewed by Moustakas and Heldin (2007). The complexity of these interactions is indicated in a recent study in hepatocellular carcinoma, which shows that sphingosine-1-phosphate (S1P) initiates PI3K/AKT signaling pathways which activates heparanase resulting in enhanced expression and activity of MMP-7 and concomitant suppression of syndecan-1. The down-regulation of syndecan-1 transiently facilitates TGF-β1 secretion, which pushes HCC cells into EMT (Zeng et al., 2016). Furthermore, a role in the modification of cell polarity by means of the regulation of epithelial polarization has been suggested for TGF-β (Ozdamar et al., 2005).

On the other hand, TGF receptor type III downstream signaling was shown to prevent EMT (Gordon et al., 2008; Meyer et al., 2014). In contrast, during heart development, the EMT of endocardial cells was found to be inhibited and their migration to atrioventricular cushion explants attenuated upon down-regulation of TGF receptor type III (Brown et al., 1999). The observed dichotomy may be relevant to differences between development and cancer or show variation in response to the specific EMT signals.

Another example of TGFβ-ECM axis was recently presented by Porsch et al. (2013). These authors show that TGFβ-dependent increase in HAS2 expression facilitates EMT execution in NMuMG mammary epithelial cells. Miao et al. (2013) identified that SPARC/osteonectin, cwcv and kazal-like domains of proteoglycan 1 (SPOCK1) are target genes for TGF-β1 and induce lung cancer cell associated EMT. TGF-β1 and EGF seem to establish crosstalk in EMT induction through synergistic increase of their intracellular mediator Erk1/2 (Tian et al., 2007). In lung and breast cancer cells, TGF-β1 transactivates EGF signaling, resulting in the activation of the downstream AKT and ERK pathways, through effects of HA and its CD44 receptor, with subsequent EMT induction (Li et al., 2015a).

Importantly, EGF treatment increases the expression levels of Snail, vimentin, and FN, while at same time the expression level of E-cadherin was decreased (Kim et al., 2016). The effects of EGF that induce EMT in breast cancer and gastric cancer cells (Davis et al., 2012; Chen et al., 2014; Bouris et al., 2015) are also associated to ECM remodeling and the regulation of the motile properties of cancer cells (Bouris et al., 2015; Voudouri et al., 2016a,b). Heparanase, an important modulator of ECM, through its heparin and heparan sulfate cleaving effects, was found to influence both FGF and TGF-β-dependent EMT (Masola et al., 2014, 2016). Furthermore, PDGF through regulating tenascin-C expression modulates ECM reorganization and EMT in bladder cancer (Berndt et al., 2015).

The Wnt/ β-catenin signaling pathway is closely associated to EMT (Volckaert and De Langhe, 2015) and specifically related to the regulation of E-cadherin adhesion properties (Buscarlet and Stifani, 2007). Recently, a key role of HA has been shown in the regulation of β-catenin–dependent tumor cell growth (Chu et al., 2016; Kouvidi et al., 2016). Moreover, the ECM1 protein has been shown to facilitate breast cancer metastasis through the stabilization of β-catenin (Lee et al., 2015). Furthermore, it has been suggested that ECM density facilitates EMT by weakening E-cadherin/β-catenin dependent cell–cell adhesions (Kumar et al., 2014). The basic aspects of inteplay among cells and the ECM during the process of EMT are depicted in Figure 1.

Conclusions

The detachment of the normal epithelial cells from matrix and subsequent phenotypic modulations attributed to the EMT has been characterized as a "hallmark" of cancer. The extremely well organized ECM suprastructure in addition to its supportive role, can process and deliver a plethora of signals to cells, that ultimately regulate their behavior. Subsequently, the ECM-derived signals are critically involved in the process of EMT during tumorigenesis. Indeed, the ECM and the EMT are connected at several levels and their fine-tuned interactions have a key role in the pathology of cancer. The roles of discrete ECM components in the process of cancer-associated EMT, discussed in this review, may suggest novel potential target molecules. Further investigation of EMC–EMT interactions may provide key insights into understanding mechanisms of cancer pathologies and enable development of focused, effective therapies for the disease in the future.

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